FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

MEETING ON INFLUENZA VIRUS VACCINE

FORMULATION FOR 1997-1998

MEETING BY TELECONFERENCE

Friday, March 14, 1997

1:50 p.m. to 2:55 p.m.

Building 29, Room 121
Bethesda, Maryland

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PARTICIPANTS

Dr. Denise Royster,
Scientific Advisors & Consultants Staff, FDA
301-827-5155

Dr. Patricia Ferrieri
612-624-1948

Dr. Gregory Poland
507-284-9039

Dr. Paul Meier
212-305-9399

Dr. Michael Apicella
319-335-7807

Dr. Adaora Adimora
919-966-2536

Mrs. Rebecca Cole
919-932-3842

Dr. Caroline Hall
716-275-5242

Dr. Claudia Dade
718-334-3969 ext. 3691

Dr. Alison O'Brien
301-295-3419

Dr. David Karzon
520-299-5488

Dr. Theodore Eickhoff
303-315-3052

Dr. Mary Glode
303-861-6982
Backup Nos. 6918/6738

PARTICIPANTS (Cont'd)

Dr. Dixie Snider, Jr.
404-639-7240

Dr. Arthur Reingold
507-281-8000

Dr. Edwin Kilbourne
203-245-9349

Dr. Ralph Vosdingh
717-839-4231

Dr. Ron Thiboutot
717-426-6255

Dr. Tony Govier
313-996-3840

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C O N T E N T S

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P R O C E E D I N G S

(1:50 p.m.)

MRS. CHERRY: Okay. Let me apologize for the delay and welcome you all to this meeting anyway.

Even though we are late, we'll try to move ahead very quickly.

Madam Chairperson, do you want to take it from here?

(Discussion off the record)

DR. FERRIERI: Well, I'll call it to order and turn it over to Mrs. Cherry for conflict of interest.

CONFLICT OF INTEREST STATEMENT

MRS. CHERRY: This is brief. This announcement is made a part of this meeting of the Vaccines and Related Biological Product Advisory Committee on March 14, 1997.

The temporary voting members for today's meeting are Dr. Ted Eickhoff, Dr. David

Karzon and Dr. Dixie Snider.

Based on the agenda made available,

it has been determined that the Committee discussions at this meeting for the formulation of the influenza virus vaccine for the 1997-98 season present no potential for a conflict of interest.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record.

With respect to any other meeting participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they wish to comment on.

And the only other item that I would add to this is, I would remind people that there is a need to identify yourself before you

speak. Our transcriber cannot see who it is that's speaking.

That's all the announcements that I have.

DR. FERRIERI: Thank you, Nancy.

Again, welcome to everyone. I want to thank you all for taking this time today for our annual review of the final decision-making on the components of next year's influenza vaccine.

I'd like to turn it over now to Dr. Roland Levandowski of FDA who will introduce the subject and, then, call upon other members participating from the CDC.

Roland, you are there?

DR. LEVANDOWSKI: Yes, I'm here. I hope you can all hear me.

A PARTICIPANT: Yes.

INTRODUCTION AND REVIEW

DR. LEVANDOWSKI: This is Roland Levandowski.

If you're ready to begin, I would

like to start with kind of a review of what has

happened in the season so far and start with

reviewing -- because there are some people -- some of the Committee members who weren't present at the January meeting, just review what happened there.

As you will all be aware, there was information that was presented on the influenza A and B viruses that are starting to develop as new strains.

And, in particular, we had information that was presented, as usual, on the strains that are antigenically divergent from the current vaccine strains, how those strains have been spreading in human population, and the responses of people who have been immunized with the current vaccines.

Based on the information that was presented at that time, at our January meeting, the recommendation was that the vaccine should continue to be a trivalent influenza virus vaccine and contain both H1N1 and H3N2

influenza A virus components, as well as an influenza B virus component.

There was a specific recommendation to select a strain for the influenza B virus component of the vaccine and that the recommendation was to retain the influenza B/Harbin/7/94 component.

That recommendation was made based on the information that we had at that time, that were not a lot of new influenza B virus strains circulating. And those that were apparent were very much like the referenced strains B/Beijing/184/93 and B/Harbin/7/94, which is a similar strain and, of course, is the strain that has been in the vaccine during this past year.

There was also information to note that there have been continued isolations of strains that are very much like the B/Victoria/2/87 virus, which is on a different lineage from the current influenza B virus -- the strain that's currently in the influenza

vaccine.

But those strains have been limited,

really, only to China. They have not been identified anyplace outside of China up to this time.

Those were represented in much of the information that was presented by a strain called B/Guangdong/5/94, you might recall.

The serologic responses of people at that time also indicated that the recent strains, with the exception of this B/Guangdong/5/94 strain, were very well inhibited by immunization with the vaccine that has currently been available.

The selection of the H1N1 and the H3N2 strains was postponed, pending collection of additional information.

And for the H1N1 viruses, there was some concern about the potential spread of strains that have a particular type of hemagglutinin, the so-called H1 deletion mutants, which would have been represented by

the referenced strains A/Wuhan/371/95 or A/Beijing/262/95.

There were reports at the time of meeting in January that suggested that these strains might be appearing in Switzerland, although up to that time there had been no report of any of those strains outside of China.

In addition, the serologic responses of people to the new H1N1 viruses that were circulating were predominantly low, as compared to the vaccine strain. And that included for such referenced strains as A/Bayern/7/95 and A/Shanghai/7 or 8/96.

For the H3N2 viruses, the predominant strains were quite clearly of the A/Wuhan/359/95 variety, that a strain like that is the one that has been in the vaccine this last year, the A/Nanchang/933/95 strain.

But there was evidence for antigenic heterogeneity among the H3N2 strains. And in particular, there were two genetic variants

that had been identified as represented by the A/South Africa/1147/96 strain and the

A/Genoa/9/96 strain.

Finally, with respect to the H3N2s, the human serologic data were not very convincing in any direction and in terms of the ability of the current vaccines to induce antibodies that would inhibit strains such as the A/South Africa/1147/96.

The concern was that one or the other of these newly identified strains might somehow be developing predominance. And therefore the decisions on those (electronic interference) strains, the H1N1 and the N3N2 were deferred.

Although it was suggested by Dr. Couch, who isn't with us today, that the A/Nanchang/933/95 vaccine component would probably be okay in view of the data that we had, had to look at, at that time.

However, the direction on the H1N1 virus was a lot less clear, and there was that concern about the potentials for the H1

deletion mutant in Switzerland.

Subsequently, the World Health

Organization held its annual consultation on influenza vaccine composition in Geneva on February 17th and 18th, and made recommendations for the composition of vaccines based on data that were current to that time.

And their recommendations were -- and this is in the handout material that had been passed out to the Advisory Committee members and should be available to people here in the room with me -- that the vaccine composition should be an A/Wuhan/359/95-like strain, which meant predominantly an A/Nanchang/933/95 strain as the actual strain; for an A/Bayern/7/95-like strain, which is a new H1N1; and for a B/Beijing/184/93-like strain, which, again, would be most likely the B/Harbin/7/94 strain as the actual strain.

The data that were used for making the recommendation for the influenza B strain were very similar to what we presented here in

21 January.

22 The data that were used for the H3N2

recommendation were augmented by some additional material that was available for the H3N2 strains.

That information continued to indicate that the circulating strains were very clearly A/Wuhan/359/95-like in all parts of the Northern Hemisphere.

But even though the A/South Africa/1147 strain and the A/Genoa/9/96-like strains could be separated out antigenically and genetically, there was not evidence that one or the other of these was becoming predominant or that it was, indeed, a predominant strain anywhere.

For the H1 viruses, the data available at that time indicated that there were no H1 deletion mutant strains in Switzerland, and therefore that was not pursued further.

The recommendation for the H1N1

strain to be an A/Bayern/7/95-like strain was

based on the fact that many of the strains

could be identified to be somewhat poorly inhibited by antisera for either the A/Texas/36/91 or the A/Taiwan/01/86 reference strains; that the A/Bayern strain itself represented genetically the consensus for all of the circulating influenza A(H1N1) strains; and that the antiserum to A/Bayern, in fact, inhibited all the currently circulating strains quite well.

That was taken into consideration along with the human serologic data, which, again, indicated that the responses from current vaccines might be reduced.

Subsequently, we've obtained some additional information about the A/Bayern strain. And that will be presented in greater detail -- or all the information on the strains will be presented in greater detail by Nancy Cox and Helen Regnery in just a moment.

But the information that we have

about that particular strain is that the named

strain itself will probably not be suitable for

use in manufacturing, and therefore a lot of the information that we will present will relate to additional strains that look like they may be strains that could be suitable.

If there are any questions or comments about what I have indicated so far, would you please make your comments or questions now.

(No response)

DR. LEVANDOWSKI: Okay. If there are no questions about that from anybody, I'd like to ask Nancy Cox and Helen Regnery if they would present some additional information on the H1N1 and the H3N2 viruses.

Are you there?

(Pause)

Nancy? Nancy Cox.

DR. COX: Hello.

DR. LEVANDOWSKI: Nancy, can you hear us?

DR. COX: Yes.

DR. LEVANDOWSKI: Okay. Are you

prepared to present some additional information on the H1 and the H3 viruses?

DR. COX: Right. Can you hear me well?

A PARTICIPANT: No. Can you all go on mute?

A PARTICIPANT: No.

A PARTICIPANT: No.

A PARTICIPANT: (Inaudible) at the FDA.

MRS. CHERRY: On FDA? Let me see.

(Pause)

Okay.

DR. COX: Okay. Can you hear me well now?

A PARTICIPANT: Better.

A PARTICIPANT: Better.

A PARTICIPANT: Yes, I'm fine.

DR. FERRIERI: You'll have to speak up, Dr. Cox.

DR. COX: Okay. I'm speaking about as loudly as I can.

DR. FERRIERI: Thank you.

ADDITIONAL INFORMATION ON H1N1 AND H3N2 VIRUSES

DR. COX: I'll be fairly brief and won't actually talk about influenza activity in the United States, unless people have specific questions, in the interest of time.

If everyone would turn to their CDC handout and turn to page 2, I'll make some very brief comments about influenza B isolates that have been analyzed since our meeting, and actually since the WHO meeting.

Rather than go through the data in any detail, I'll just summarize by saying that any subsequent testing for influenza B has been very reassuring. And the bottom line is essentially that nothing has changed since our January meeting, and our selection of the Harbin strain looks very solid.

We have received quite a number of influenza B isolates from the United States and

know that there has been quite a bit of B

activity in Europe as well.

And if you would now turn to page 4, I believe that Roland has clarified information that was presented at the January meeting concerning the deletion mutants, represented in this test for -- by Antigen No. 5, the A/Beijing/262/95 strain. And now we believe that these strains have been seen only in Asia.

You'll note that Antigen No. 4 is the Bayern virus that Roland mentioned and had talked about at our January meeting as well.

And you will see that this virus, like a number of the other test antigens in this particular HI test, are reduced four-fold, are greater in titer when compared with the tests of homologant titers in column number 3, going down the page.

Likewise, on page 5, you will see we have an HI test with the Texas antiserum in column 3. And you'll see that there a number of antigens here which have titers which are

reduced four-fold or greater compared to the tests with homologant titer.

In lanes four through six, we have three vaccine candidates, Shenzhen/227, Moscow/1, and Johannesburg/82, which cover the antigens which are reduced in titer with the Texas (electronic interruption) much, much better.

In particular, at the moment, we're focusing on the Shenzhen/227 and Johannesburg/82 as potential vaccine candidates. And Roland will have some comments about these particular strains later on.

Does anyone have any questions about the antigenic profiles of the virus?

DR. KILBOURNE: Nancy, this is Ed Kilbourne.

Could I just point out that I set up some titer ratios here, and that if we go back and compare the antigenic relationship of Taiwan to the Texas, they are 50 percent -- I'm sorry, they are 35 percent related.

The relationship of Texas now to Shenzhen/227 shows a 50 percent relatedness. I

thought this might be a good point to put down on the table while you have the ratios in front of you.

DR. COX: Okay. Thanks very much.

So there's a similar distinction between Taiwan and Texas?

DR. KILBOURNE: Well, it looks like the Texas and Shenzhen are a little bit more close than when we made the change from Taiwan to Texas is what I'm saying.

DR. COX: Okay. If we go on to page 6, this table has actually changed very little. The only additional isolates that we've had to analyze since we met are five isolates: One which fell into the Texas-Taiwan category during the April to September time period, and four additional ones which fell into the Beijing/262-like category from that same time period. Those are the only additional data that we have.

If you'll turn to page 7, what we have done here is to focus just on viruses,

determining the frequency that we're seeing viruses with reduced HAI titers to the Texas vaccine strain.

And, of course, because we haven't had very many recent H1N1 strains, we had to look back in time to the period October 1, 1995, to September 30, 1996.

And we see that there are, overall, about 30 percent of strains which are reduced, in titer to the Texas strain, four-fold or more.

In the United States last year, the same reduced in titer, four-fold or greater.

And if you look at what was occurring in South America, particularly during their winter season -- this past summer for us -- about 57 percent of the strains that we characterized were reduced four-fold or greater in titer.

On page 8, you'll see the adults of

our human serology, the one test that we did since the FDA meeting.

And, again, as Roland had mentioned in his introductory remark, we see a reduction in post-vaccine GMT with the Bayern strain of about 50 percent.

If we move on and look at the genetic analysis on page 9, you will see the dendrigram for the HA nucleotide sequences.

And what becomes very clear is that, on a genetic level, you'll see that the Texas strain, which is shown up at the top but in the middle of the page, the Texas/36/91 strain, had moved on quite a lot genetically from the Taiwan/86 strain; and that current strains on here, on the right-hand side of the page, have moved on considerably in their HA nucleotide sequences from the Texas strain.

And what we have -- you'll see that there are actually two lineages of current strains. The one at the bottom is representative of the deletion mutants. And

once again, those have just been seen in Asia.

DR. FERRIERI: Pat Ferrieri.

Dr. Cox, I couldn't find Johannesburg on this dendrigram. Is it here?

DR. COX: No, it is not. It was sequenced by our colleagues in Mill Hill.

But it does belong in the group of -- the small group of three viruses from Durban, South Africa -- from Africa that are shown -- that are a little bit farther out on the evolutionary --

DR. FERRIERI: I see them, yes. Thank you.

DR. COX: What we have noted about the currently circulating H1N1 strain, apart from the deletion mutant, is that they -- many of them have sequences very close to the consensus sequence. There seems to be a bit less variation at the amino acid level among the H1N1 than among the H3N2.

If you turn to page 10, the evolutionary relationships among the

21 nurminadase (phonetic) genes of the H1N1

22 viruses.

And their thing (electronic interruption) they had made about the -- that is, these circulating claims (phonetic) have nurminadases that are actually more closely related to that of Taiwan than that of Texas. And you could see the nurminadases of the Bayern/7, Moscow, first Shenzhen viruses are there.

So, in summary, we haven't had many new H1N1 viruses to examine. There have been so few viruses isolated worldwide.

Overall, viruses appear to have directed somewhat, both antigenically and genetically, from the current Texas (electronic interference). And this is reflected by about 30 percent of viruses being down four-fold or more with the Texas antiserum.

(Electronic interference) in our hands showed a 50 percent reduction in GMT for the Bayern (phonetic) antigens, as compared

with titers for the vaccine strain itself.

Are there any questions?

DR. KILBOURNE: Nancy, Ed Kilbourne again.

Do you have any data on the antigenic relationship of the norminadase (phonetic) genes, their gene products?

DR. COX: No, we don't.

DR. KILBOURNE: Okay. So that's -- at the moment, that's interesting phylogeny, but we don't know the relevance to the question.

DR. COX: We don't know how different they are antigenically. But -- and whether or not the changes are in antigenic -- previously recognized antigenic areas, and there are some changes.

DR. KILBOURNE: We see a lot of similarity between the nurminadases in Texas and Taiwan. So maybe that will.

DR. COX: Okay.

I'll move on to the N2 viruses, the

HI test on page 11. And it demonstrates pretty much what Roland mentioned earlier, that plenty

of viruses look Wuhan were Nanchang-like in their antigenic profiles.

There is, however, antigenic heterogeneity, as reflected in antigens such as the South Africa strain.

However, I have looked very carefully at correlating the antigenic and genetic information, and there is really no clear direction at the moment for the evolution of these viruses.

So there are many viruses which are a genetic group represented by Wuhan. And there are viruses -- recent viruses that are a genetic group represented by South Africa, and also in a genetic group represented by Genoa. None of these groups seem to be winning at the moment.

I don't think there's any point in dwelling very much on the HI table on page 12. It shows a very similar picture to that you've

already seen.

And we can turn on to page 13. And

you can see that we analyzed 257 influenza A(H3N2) isolates during the period October '96 through the end of January '97 -- actually, to the current time. And the majority of these strains are Wuhan-like.

Reflected again on the table on page 14, they're similar (inaudible) to the way we seated our data for the H1N1 strain. And we have just looked at the frequency of reduced HAI titers to the Nanchang vaccine strain.

And we are, as we -- from the data and as we mentioned before, you can see some viruses with a titer that's four-fold reduced, but the percent is much smaller.

And I'd like to stress once again that there's no clear direction (inaudible) either antigenically or genetically to where these viruses are going at the moment.

That concludes my comments.

Unless there are any questions, I'll

turn the floor back over to Roland.

DR. LEVANDOWSKI: Okay. Thank you.

Can you hear me?

A PARTICIPANT: Yes.

A PARTICIPANT: Yes.

DR. LEVANDOWSKI: Okay. Good.

A PARTICIPANT: Yes.

DR. LEVANDOWSKI: I would just like to very briefly go through some additional data.

There is a handout, a very short one, from CBER. The first two pages of that handout are a reiteration of the H1N1 hemagglutination inhibition antibody titers that we presented in January.

There is not new information from us on that. But it just reinforces, looking very quickly at the tables for both elderly and adults, that we have been seeing reductions in antibody responses to these newer strains like A/Bayern/7/95, and limiting the discussion to that and ignoring the H1N1 deletion mutant at

the moment.

The last two pages of the handout

contain some information about the strains that are available at this point. And there's a typo on each one of the pages. The strain designation should be A/Perth/13/95. Sorry about that.

There are a number of potential vaccine candidate strains that are available at the current time for the H1N1.

The information on A/Perth/13/95 is not complete at this point, so perhaps I shouldn't say that it's an A/Bayern-like strain. But it is a strain that is being looked at as a potential candidate to fill that role, and that needs some confirmation.

There is a high-growth reassortant from CSL, IVR-92, which is listed here.

In addition, at the current time -- and this information is changing daily -- we have information that there are at least four candidate reassortants available for either

21 A/Shenzhen/227/95 or for A/Johannesburg/82/96.

22 Dr. Kilbourne's laboratory, I

believe, has an A/Shenzhen/227/95 reassortant candidate?

DR. KILBOURNE: Yes.

DR. LEVANDOWSKI: Our laboratory has an A/Johannesburg/82/96 high-growth reassortant candidate.

And the NIBSC has one of each of those. Those strains are at a relatively early stage of being looked at. They have not yet gone into ferrets (phonetic). They have not yet been confirmed that they're antigenically correct.

So we're at a stage where we really don't know whether any of these will turn out to be a proper vaccine candidate. But with four of them, the chances or the prospects for that being true seem to be particularly good.

In addition, there is the A/Perth/13/95 high-growth reassortant that also needs to have some confirmation, which could be

a candidate strain.

There really isn't information about

any of these strains in terms of their growth characteristics, because none of them to this point have been distributed to any manufacturers.

And therefore I would like to turn just briefly to the wild-type strains for those. We do have some information at the moment on both the A/Shenzhen/227/95 and the A/Johannesburg/82/96 strains, and those appear to be relatively low in their growth potential.

The comparison that I've been hearing is that they would be very much like the A/Taiwan/1/86 strain, which was used for the vaccine but was not -- I'll remind you that there was not a high-growth reassortant for that particular strain.

And the yield from that strain was acceptable but low, at a time when there were probably about 20 million doses of vaccine being produced for the United States, as

compared to now, when there are upwards of 70 million doses of vaccine being produced.

There is some additional information in here, in the package on the H3N2 strains, at least in terms of the reassortants, but I don't really want to go into any of that at this point.

I might ask if there are any questions or comments about the strain availability.

And if there aren't questions or comments from the Committee members, I would like to ask the manufacturers if they would be prepared to give some comments.

Are there any questions from the Committee?

(No response)

DR. LEVANDOWSKI: If not, are there any manufacturers who have some information that might be relevant to the strains that I was just discussing, the H1N1 strains, the Shenzhen/227/95, the Johannesburg/82/96, or the

Perth/13/95?

(No response)

DR. LEVANDOWSKI: If I'm not hearing anything, I will take that to mean that those of you who are out there agree with what I said already to this point and that there's not any new information to add yet.

I would emphasize that we are at the stage of scrambling to try to get this information together, and everybody is working quite hard to try to fill in the blanks that still exist for the strains.

I would point that -- and maybe Nancy Cox will want to comment on this as well -- the strains that -- if they haven't gone into ferret yet to be able to determine their antigenicity or their antigenic profile for using a serum from the specific strain, it takes two to three weeks to get the serum from the ferret to be able to test.

So that to have full confirmation on this, or to be as certain as we can be about

the strains, we wouldn't have that information for at least two weeks, if we're very lucky.

DR. POLAND: This is Greg Poland.

When you say that these wild-type strains still require confirmation, do you mean the latter point that you just made, or that it's not sure that these are high-growth from the manufacturer's point of view?

DR. LEVANDOWSKI: The wild-type strains don't need antigenic confirmation, as far as I know. We would -- of course, the seed viruses, as they come from the manufacturers, would require testing to be sure that they haven't changed in some way antigenically.

I was really referring more to the high-growth reassortants, which may have some mutational event in the reassorting process that might render them unacceptable.

DR. POLAND: Okay. I understand now.

DR. LEVANDOWSKI: Okay. I have one other piece of information that might be useful for the Committee.

The Europeans had their meeting this week on Tuesday and Wednesday to discuss strain

selections for Europe, and that included both the national laboratories that would be involved in this, the national authorities, and the manufacturers.

And the information I have is that they agreed that they would use, in Europe, strains that fit the WHO recommendations. And in terms of the strains that they would find permissible to use that would fit the description, the A/Nanchang/933/95, RESVIR-9 strain was accepted as a Wuhan/359/95-like strain. So it most likely means that that strain will be used for manufacturing in Europe.

The B/Harbin/7/94 strain was accepted as a Beijing/184/93-like strain for the purposes of WHO recommendations.

And finally, the A/Shenzhen/227/95 and the A/Johannesburg/82/96 strains were both accepted as being A/Bayern-like. That's the

wild-type, not to be confused with the high-growth reassortants that are still in the

process of being tested fully.

One further piece of information that I think will be useful is that information from Europe, from manufacturers in Europe, is that they, too, find -- or they all find, unanimously, that there is not a problem with stability of vaccines that have been manufactured with the A/Nanchang/933/95 virus.

I think at this point I would just maybe like to summarize and then ask for Committee input and discussion and recommendations.

What we see before us, in terms of the H1N1 virus, is pretty much as it was in January, that we see that there are strains that can be determined to be antigenically and genetically different from the current vaccine strain; that the antibody responses of people who have been immunized with the current vaccines are reduced to some of those current

vaccines -- some of those currently circulating strains.

And there do appear to be, at this point, strains that very likely will turn out to be acceptable for manufacturing -- new strains that will turn out to be acceptable for manufacturing.

In terms of the H3N2 viruses, again we have filled in some of the blanks that we had in January, but the data have not changed all that drastically.

The strains that are circulating appear to be predominantly A/Wuhan/359/95-like.

There is some antigenic heterogeneity that's occurring.

Strains can be determined to be somewhat different, but not that different from the vaccine strain.

And there is also some variability in the responses, the human serologic responses, but not to the extent that it indicates that there is not an antibody response to the

majority of the currently circulating strains.

I suppose there are some options for

both of these remaining strain selections. Of course, for the H1N1 strain selection, the first option would be to make no change at all.

For that would be that we know very well what the manufacturing capacity would be for that strain, that all of the pieces are in place for doing the manufacturing.

But against that would be we do have information that suggests that the H1N1 strains are moving on antigenically, and perhaps to the point of not being very well recognized by the current vaccines.

The other option is to change that strain, and the actual strain to select would be open to some further discussion.

In favor of the strain selection would be that we would have a strain that would be more closely related to the currently circulating strains.

Against that would be that we do have

some uncertainties about whether we actually

get one of these strains that can be used to

make as much vaccine as we'd like to see made for the United States.

And I suppose there could be a third option, as a contingency, that we would want to -- or the option could be that the recommendation could be for changing the strain unless we can't find a strain that is antigenically suitable for manufacturing.

For the H3N2 strain, there also are probably basically two options. One would be not to change. And again, in favor of that would be the fact that there is a lot known about manufacturing with this particular strain.

The strains that have been identified to this point are predominantly very much like the current vaccine strain. And it's not clear from the serologic responses that we would gain anything by a change. We actually wouldn't know what the responses would be if we made a

change at this point.

Against that would be that we do know

that the H3N2 viruses are continuing to change, that that's very apparent from the data.

But, at this point, I guess I'll stop and ask Dr. Ferrieri to lead the Committee discussion and make the recommendations to answer the questions. And the two questions are as they are shown on the agenda.

The first one is, what strain should be recommended for the influenza A(H1N1) component of the vaccine?

The second question is, what strain should be recommended for the influenza A(H3N2) component of vaccine?

DISCUSSION

DR. FERRIERI: Thank you very much, Roland.

I'd like to encourage Committee members who are on line here to ask you or Dr. Cox or anyone else questions at this point.

No one has seemed to have -- no one

seems to have very many questions, because many people have had the opportunity to hear some of

the data earlier.

And we appreciated the organization and the relative brevity of what you said at this time. Thank you very much.

Committee members, are there any general or specific questions?

DR. POLAND: This is Greg Poland. I have one for Roland or Nancy.

Are you persuaded at all by the apparent finding of a greater circulation of influenza B isolates in China and, I guess, actually throughout Asia, and at least toward the end of the season some changes that are different than the B/Harbin?

DR. COX: I'll try to answer that question, Greg.

We do see the Victoria strains circulating in Asia, as is reflected in the table -- frequency table on page 3.

The Victoria-like strains have been

circulating in China and Hong Kong without

detection (electronic interruption) since

before. And we have to remain vigilant and keep the reagents available for people to identify these (electronic interruption).

Outside of China, I think, we're just in status quo, in a very similar situation (electronic interruption) that we've had for a number of years.

DR. MEIER: Excuse me, I have to go. This is Paul Meier.

DR. FERRIERI: Yes, Dr. Meier. Sorry that you have to. Thank you for hanging in there this long.

DR. MEIER: Not at all. Bye now.

DR. FERRIERI: Bye.

DR. ADIMORA: (Inaudible) interrupt. This is Ada Adimora. I just want you to know that I am here.

DR. FERRIERI: Good. Thank you.

DR. ADIMORA: Thank you.

DR. BARDAY: And this is Mimi Barday

(phonetic). I'm here too.

DR. FERRIERI: Oh, good. I was going

to check later.

Thank you.

Dr. Dade.

(Pause)

Dr. Dade. Hello.

DR. DADE: Yes. This is a very simple question, related to this issue of, you know, seeing some other strains of B virus circulating.

Can any intervention be made later if it seems that what you had is a real held wave -- you know, that you have some virus that is circulating and that is, then, going to, you know, possibly become epidemic in the flu season?

Is this the final decision with regard to the -- you know, the constituent strains for the vaccine?

DR. LEVANDOWSKI: This is Roland Levandowski. Could I maybe answer that

question?

DR. FERRIERI: Please, Roland.

DR. LEVANDOWSKI: It's not the end. We always could bring the Committee back together in the event that there were other strains that were identified that were thought to be significant health risks. That has been done in the past.

You might recall the Taiwan/1/86 strain actually was originally made as a supplemental vaccine strain. It was identified very late in the year in March of 1986, I believe.

And there were some very -- I wasn't here at the time, so I am not speaking from experience, but there was a lot of work that was done to make a recommendation for using that strain in certain age groups and then to try to make the vaccine.

The vaccine, as you might recall, was produced very late in the year. It didn't get out to -- into distribution until probably

November or even into December, and therefore it did not have a lot of impact on prevention

of influenza in that particular year.

The manufacturers, I believe, did not feel that that was a particularly productive event for them either, in terms of trying to make that vaccine and then seeing most of it not used because of -- partly because of the timing, partly because of confusion about what group should be receiving the vaccine.

It required supplemental recommendations from ACIP, for example. And that information got to the clinic level in -- possibly too late for people to recognize what to do.

So there was a lot of confusion that year.

DR. DADE: I understand.

DR. LEVANDOWSKI: It is possible to do that, and we do keep that in mind. And, in fact, that is part of being able to be prepared for a pandemic if it should appear, a new

strain that shows antigenic shift from the current influenza A strains.

DR. DADE: Thank you.

DR. FERRIERI: (Inaudible) any other questions? Otherwise, I would propose that we address the easier of the questions, to begin with that is -- and that is our recommendation for the H3N2, the flu A(H3N2) component of the vaccine.

Do I have any motions regarding our conclusions and recommendations for FDA and the manufacturers?

DR. SNIDER: This is Dixie Snider.

(Electronic interruption)

DR. FERRIERI: Hello.

DR. SNIDER: Can you hear me?

MRS. CHERRY: Now, Dixie, yes.

DR. SNIDER: I did not see a reason -- a compelling reason to make a change in that component of the vaccine for the coming year, so I would move to keep the H3N2 strain the same.

DR. FERRIERI: Thank you.

Is there a second?

DR. APICELLA: I would concur with that.

DR. FERRIERI: Thank you, Mike -- Dr. Apicella. Thank you, Committee members.

Any further discussion before we take a formal roll call of a vote for that motion?

(No response)

DR. FERRIERI: Dr. Poland.

DR. POLAND: Yes, I agree.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: I agree.

DR. FERRIERI: Dr. Adimora.

DR. ADIMORA: I agree.

DR. FERRIERI: Mrs. Cole.

MRS. COLE: I agree.

DR. FERRIERI: Dr. Caroline Hall.

DR. HALL: I agree.

DR. FERRIERI: Dr. Dade.

DR. DADE: I agree.

MRS. CHERRY: Oh, Dr. Dade is not a

voting --

DR. FERRIERI: A voting --

Okay. Yes, forgive me.

Nancy, please correct me if I've called on anyone incorrectly here.

MRS. CHERRY: Okay.

DR. FERRIERI: Dr. O'Brien.

MRS. CHERRY: No. She's not a voting member.

DR. FERRIERI: And Dr. Karzon -- David.

DR. KARZON: I agree.

DR. FERRIERI: Dr. Eickhoff.

DR. EICKHOFF: I agree.

DR. FERRIERI: And Dr. Glode is not a voting member anymore?

MRS. CHERRY: No, no.

DR. FERRIERI: Dr. Snider is.

MRS. CHERRY: Yes.

DR. SNIDER: I made the motion, so --

DR. FERRIERI: Correct. I don't think I have missed anyone. And my own vote is

yes.

Anyone that I've missed, Nancy?

MRS. CHERRY: No. That's it.

DR. FERRIERI: Thank you.

We'll move, then, to what is a muddier area now, and that is for the H1N1 component. You've heard extensive data and (inaudible) of the situation that we have in the laboratory regarding strains that look promising antigenically but that appear at the moment to be low-growth potential.

Do we have spontaneous remarks for recommendation?

You might recall that the focus has been on these two wild strains, the A/Shenzhen and the A/Johannesburg, possibility of a Perth/13/95, but there's not very much information there.

But there are these at least two candidate strains that may or may not be promising for actual use then.

DR. REINGOLD: Pat, before we go

on -- this is Art Reingold (inaudible).

DR. FERRIERI: Yes.

DR. REINGOLD: I want to try and go to the airport --

DR. FERRIERI: Fine.

DR. REINGOLD: -- (inaudible) planes are leaving here in Rochester. So --

DR. FERRIERI: Thank you so much, Art. Is there anything you would like to add before leaving?

DR. REINGOLD: No.

DR. FERRIERI: Okay. Take care.

DR. REINGOLD: Thanks.

DR. FERRIERI: Bye.

DR. REINGOLD: Bye.

DR. KILBOURNE: This is Ed Kilbourne, and I can give some supplemental information on the Shenzhen --

DR. FERRIERI: Yes.

DR. KILBOURNE: -- because in our lab, I think it grows very well, almost like the wild-type Taiwan, which was used before.

And recombinant is even better.

Of course, we're just in the early

stages, as Roland said, of characterizing this. But I would feel that even if one had to fall back on the wild-side, that it's really growing better than the experience at CBER would indicate.

I don't know what the difference is, and we've got to prepare notes on this. But I just -- I just would like to introduce that information in the background of discussion.

DR. APICELLA: Pat, I'd like to hear from the manufacturers about this, in terms of what they think.

DR. FERRIERI: Yes. Thank you, Mike.

Dr. Vosdingh from Cannard (phonetic) or Dr. Thiboutot from Wyeth.

DR. VOSDINGH: This is Ralph Vosdingh at Cannard.

The Manufacturing Department has passed both of those strains, and (electronic interruption) of the wild-types. And they

think they have (electronic interruption)

satisfactorily.

DR. FERRIERI: The Shenzhen and the Johannesburg, Dr. Vosdingh?

(Pause)

Any other comments from Wyeth or Parke-Davis?

DR. THIBOUTOT: Yes. This is Ron Thiboutot. The Johannesburg that we've run and the Shenzhen that we've run, they grow far worse than the Texas of last year. So this would create some probably significant problems in getting vaccine out if we were to go into either one of these right now.

DR. FERRIERI: You need wild -- wild strain, the wild strain?

DR. THIBOUTOT: Yes.

DR. FERRIERI: Thank you, Dr. Thiboutot.

Other questions or comments from the Committee? I suspect we're not going to be able to make any firm recommendation to FDA and

that we may have to leave it hanging, depending on the data that comes in.

If it's satisfactory, then one would move ahead with one of them.

But, then, you might remember, Committee members, the contingency plan that is possible. And that would be to stay with the A/Texas/36/91-like strain. That wouldn't be the end of the world from my perspective.

DR. EICKHOFF: Pat.

DR. FERRIERI: Yes.

DR. EICKHOFF: This is Ted. I would -- my thinking was very much in the line that you were just moving in. And I would favor -- if we need to have a motion, I would favor sort of a permissive motion that urges that all possible effort be made to update the H1N1 component.

And if it turns out there is a not a good producing strain, to fall back on the current strain.

DR. KARZON: I would second that.

DR. FERRIERI: Yes.

Well, we now have a formal motion. I

like it.

It was stated very well. Thank you so much, Ted. I think that couldn't be summarized better in terms of an intelligent position for us to take.

Other discussion before we would vote on the motion?

(No response)

DR. FERRIERI: Committee members or anyone else who would like to --

DR. THIBOUTOT: Well, again, I'd like to (inaudible) the manufacturers about this delay in terms of giving them that third strain, what is it going to do to them, are they going to have real problems?

MRS. CHERRY: Would you identify yourself.

DR. THIBOUTOT: This is Ron Thiboutot from Wyeth.

Strain in about four weeks max, so

that's about the time frame that you have for us to not cause any delay of product to market.

DR. EICKHOFF: Okay. So we have four weeks then.

DR. THIBOUTOT: For us to have something that we can actually use to put in eggs to make vaccine.

DR. EICKHOFF: Right. Okay.

So will we have answer in four weeks to the questions we're posing?

DR. COX: Yes. I think we will have an answer. I spoke with the folks at NIBSC this morning, and they have already put heads of their two (inaudible) and (inaudible) into ferrets. Ferrets (inaudible) will therefore be ready in two weeks' time.

DR. EICKHOFF: Okay.

DR. FERRIERI: Thank you, Dr. Cox.

DR. KARZON: This is David.

Dr. Levandowski really stated what we're trying to address at this moment about H1, namely that option one is no change; that

option two is change to selected candidates that have already been selected if they prove

suitable.

Now, can we vote in this fashion and leave this somewhat open-ended, or shall we vote to give a specific authority for the CBER in CDC groups to make a final selection among some named candidates?

DR. FERRIERI: Well, Dr. Karzon, this is my understanding on my motion that we have on the floor. It would be permissive and give them that opportunity and flexibility.

DR. KARZON: All right.

DR. FERRIERI: Is there anyone who doesn't think that this would meet with Dr. Karzon's suggestion?

DR. KARZON: I agree. That's the way I interpret it.

DR. FERRIERI: This is how we interpret it, Dr. Karzon. You're right on target. And we have such a motion in front of us now.

Other open discussion from the Committee members or anyone else?

DR. SNIDER: This is Dixie Snider. Just some clarification.

I think I'm in favor of this particular motion, but in following through on the comments that have been made, the goal would be that there would still be one strain that would be selected for both manufacturers -- utilized.

Are we talking about different manufacturers having different options?

I don't think it's the latter, but I wanted to get clarification on that point.

DR. FERRIERI: I think that your discussion point is very well-taken.

It's implicit in our motion -- and we could have an addendum to it -- that we would come up with a uniform decision with one strain that would fit all takers, that it would be uniform, and the decision obviously would have consensus, that there would be one choice then.

DR. EICKHOFF: This is Ted.

That was certainly the intent of my

motion, yes.

DR. FERRIERI: Thank you, Ted.

(Pause)

Any other point? Anyone who feels uncomfortable -- FDA -- uncomfortable with our motion?

Dr. Levandowski, is this suitable for you and the team?

DR. LEVANDOWSKI: Yes. I think the motion, as I understand it, sounds very suitable.

I just wanted to emphasize that the production of the vaccines is dependent upon having the reference reagents for doing this, also.

And I didn't mention, but we will -- with a strain change, we will have to have a new antiserum.

I don't think that we have the wherewithal at the moment -- or the time,

really -- to try to make many different

reagents. So that what it will come down to

is, in fact, a single strain that all the manufacturers would uniformly be using.

And the motion, as it was stated, to be permissive, that change to a new -- or to update the H1N1 component; but if all of that falls through for some reason, which is a possibility but not a very strong one at this point, that we would have the option to continue to use the Texas strain that's currently in the vaccine.

I think that would be very suitable from our perspective here at FDA.

DR. FERRIERI: Thank you, Roland.

(Pause)

Well, I suggest, then, if there is no further discussion, that we do our formal vote on what you've heard discussed and this motion that gives them flexibility, that would permit them, based on the data that will be accumulated in the next few weeks, to come up

with one strain, to have the reagents. And if this should fail, then we would use the current

H1N1, A/Texas/36/91-like strain.

Okay.

Dr. Poland.

DR. POLAND: Agree.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: I agree.

DR. FERRIERI: Dr. Adimora.

DR. ADIMORA: I agree.

DR. FERRIERI: Mrs. Cole.

MRS. COLE: I agree.

DR. FERRIERI: Dr. Hall.

DR. HALL: I agree.

DR. FERRIERI: Dr. Dade.

DR. DADE: I don't -- I believe I don't vote?

DR. FERRIERI: Oh, you're not voting, right. I'm sorry.

MRS. CHERRY: Dr. Karzon is the next one.

DR. FERRIERI: Dr. Karzon.

DR. KARZON: I agree.

DR. FERRIERI: Dr. Eickhoff.

DR. EICKHOFF: Agree.

DR. FERRIERI: Dr. Glode --

DR. GLODE: I think that --

MRS. CHERRY: No.

DR. FERRIERI: You're not voting.

Dr. Snider.

DR. SNIDER: I agree.

DR. FERRIERI: And I, for the record, vote yes as well.

Have I missed someone, Nancy?

MRS. CHERRY: No. That's it.

DR. FERRIERI: Thank you.

Well, the major purpose of our teleconference has been accomplished. Are there further comments?

Dr. Levandowski, do you have anything that you would like to close with? Otherwise, then, we will have opportunity for any other open remarks.

DR. LEVANDOWSKI: I would like to say

that we are proceeding with all haste to try to answer the H1N1 question, that the work has

been going on continuously since we met the last time, in January. And it will continue to go on until we get the answer.

I just want to give reassurance, I guess, in that respect.

DR. FERRIERI: Yes. Thank you, Roland.

I guess I would like to publicly state that this quandary that we're in is not due to failure of energy, time, commitment, et cetera. It's just the luck of what we're dealing with right now.

And so I applaud all the work that has been done, the haste that you've been using, and appreciate the pressure that you're all under.

And I would also ask indulgence of the manufacturers, because we appreciate the pickle that you're in as well, and hope that this will come to closure very soon.

Mrs. Cherry, do you have anything now that you would like this to say?

DR. POLAND: I'm sorry, Pat. This is Greg Poland.

DR. FERRIERI: Yes.

DR. POLAND: Did we agree that the B strain would be Harbin?

DR. FERRIERI: Yes. That was agreed upon at our meeting in January.

DR. POLAND: Okay. I missed that one. I'm sorry.

DR. FERRIERI: That's all right.

Mrs. Cherry.

MRS. CHERRY: The only thing I have is to thank all of you, and then we will move to the open public hearing.

At this time I will open the floor to anyone who wishes to make a statement for the record.

(Pause)

Denise, would you check to see if there's anyone in the hall. We're a few

minutes ahead of the scheduled time.

(Pause)

DR. ROYSTER: No.

MRS. CHERRY: No. There's no one in the hall. There's no one here expressing any interest in making a statement, so I will return the control of the meeting to you.

DR. FERRIERI: Thank you very much.

I want to thank everyone and appreciate everyone reviewing the data. And for Committee members, I looking forward to seeing all of you in April.

Thank you so much, Nancy, for all your help.

MRS. CHERRY: And thank you.

DR. FERRIERI: Bye-bye.

A PARTICIPANT: Bye.

MRS. CHERRY: Thanks to all of you.

A PARTICIPANT: Bye.

MRS. CHERRY: Bye-bye.

DR. FERRIERI: Thank you.

Good-bye.

PARTICIPANTS: Bye.

DR. FERRIERI: Thank you.

Good-bye.

(Whereupon, at approximately 2:55 p.m., the TELECONFERENCE was concluded.)

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